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Lymphoma: a clinical view

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Introduction

The lymphomas are a heterogeneous group of malignancies derived from lymphoid tissue. They consist of a number of distinct disease entities with varying natural histories and prognoses. Great advances have been made in the clinical management of lymphomas. A better understanding of the histopathology and immunology has led to improvements in the diagnosis and classification of the disease. Improvements in treatment, including dose intensification and the development of novel therapies, have contributed to increased survival. Advances in conventional and functional imaging have helped to optimize the management of lymphoma, not only in diagnosis and staging, but also for response assessment and detection of disease relapse.

The histopathology and classification of lymphomas

Virchow first coined the term 'lymphoma' in 1862 but it was not until the turn of the last century that Reed and Sternberg first recognized the importance of histology in the diagnosis of lymphoma. In 1942 Gall and Mallory proposed the first purely histological classification[1]. By 1982 there were six major classification systems in general use. One of the most important events in modern lymphoma management during the last decade has been the development of the REAL (Revised European and American Lymphoma) classification system, and its subsequent modification and acceptance by the WHO[2,3]. The REAL/WHO classification system delineates disease entities based on morphological features and immunophenotype, as well as stage of differentiation, aetiology, epidemiology and clinical behaviour. Accurate pathological diagnosis is at the heart of optimal clinical management and the REAL/WHO classification has provided clinicians around the world with a robust mechanism by which this can be achieved.

Prognostic indices

A number of attempts have been made to identify prognostic factors, including cytogenetic, tumour-related and patient-related variables. An important development has been the formulation of the International Prognostic Index, originally validated in intermediate grade non-Hodgkin's lymphoma[4]. The significant prognostic variables identified were age, stage, performance status, serum LDH and the number of extranodal disease sites. The importance of this index lies in its ability to reliably and easily identify poor prognostic groups, which may then be considered for innovative or more aggressive treatment approaches. As with the REAL/WHO classification system, the IPI also facilitates comparisons in outcome between study populations. It has subsequently been found to be useful in low grade non-Hodgkin's lymphoma and peripheral T cell lymphomas.

The initial management of lymphomas

The majority of patients with lymphoma will require chemotherapy as part of their initial management. However, the choice of treatment modality is dependent on the stage and sub-type of disease. There has been a move towards combined modality therapy (both chemotherapy and radiotherapy) in the treatment of early stage disease in both Hodgkin's and non-Hodgkin's lymphoma. Two important studies have demonstrated an advantage in combined modality therapy over chemotherapy alone in non-Hodgkin's lymphoma. Glick *et al.* observed an improved disease-free survival and failure-free survival in patients treated with eight courses of standard CHOP chemotherapy followed by radiotherapy, compared with those not receiving radiotherapy[5]. Miller *et al.* demonstrated a survival benefit in patients treated with a short course of chemotherapy (three courses of CHOP) followed by radiotherapy, in comparison with those receiving a standard course of CHOP without additional radiotherapy[6]. Similarly, combined modality therapy has been shown to be extremely effective in the treatment of Hodgkin's disease. In addition to being an effective therapeutic approach, it appears to reduce long-term toxicities such as end-organ damage, infertility and second

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malignancies. The treatment of advanced stage lymphoma largely relies on combination chemotherapy alone. Designed in 1973, the 'standard of care' for patients with advanced Hodgkin's disease remains ABVD (a regimen containing adriamycin, bleomycin, vinblastine and dacarbazine). Promising new combination chemotherapy regimens, such as the Stanford V and BEACOPP, are presently being evaluated in Phase III studies[7,8]. It remains to be seen whether there is any improvement in efficacy over ABVD, and importantly whether the toxicity profile, both short and long term, is comparable. CHOP chemotherapy was also developed in the 1970s and is still the standard first-line treatment in non-Hodgkin's lymphoma. A number of other regimens, such as m-BACOD, ProMACE-CytaBOM and MACOP-B, have been developed and tested since then but none have been shown to be superior to CHOP in randomized comparisons[9].

High dose chemotherapy and autologous transplantation

Despite the apparent lack of progress in the first-line management of lymphomas, recent advances have been made in the treatment of relapsed disease. Patients who relapse following initial therapy generally have a very poor prognosis, and treatment with conventional dose chemotherapy is unsatisfactory. Improvements in supportive care, and the development of autologous stem cell transplantation has led to the widespread acceptance of high-dose chemotherapy in such patients, and there now exist randomized data to support its use. The PARMA study investigated the role of HDT in chemosensitive relapsed intermediate and high grade NHL[10]. Patients achieving a complete response following a limited course of conventional salvage chemotherapy were randomized to receive either further conventional chemotherapy or HDT and autologous bone marrow transplantation. Both event-free survival (EFS; 46.1% vs 12.1%, $p=0.001$) and overall survival (OS; 53% vs 32%, $p=0.038$) at 5 years were superior in the high dose arm. Similar data exist for patients with relapsed Hodgkin's disease. The BNLI study published in the Lancet randomized poor prognostic patients in first relapse or with primary refractory disease between HDT and conventional salvage chemotherapy[11]. Despite no significant OS advantage at 34 months, there was a highly significant EFS advantage in the high dose arm (53% vs 10%, $p=0.025$). The study was closed early because subsequent patients refused randomization into the conventional salvage arm. There are ongoing studies in both Hodgkin's and non-Hodgkin's lymphoma that are designed to optimize the timing of high-dose chemotherapy. In addition several studies are testing the hypothesis that high-dose chemotherapy and transplantation has a role to play in the treatment of poor prognostic patients, instead of conventional chemotherapy.

Novel therapies

Advances in biotechnology have facilitated the development of novel therapies designed to function at both a cellular and genetic level. One such example is the monoclonal antibody, rituximab. Rituximab is a genetically engineered, chimeric monoclonal antibody that binds specifically to the B-cell surface antigen, CD20. This epitope is expressed on over 95% malignant cells in B-cell NHL. It exerts its therapeutic effect via activation of the immune system and by induction of apoptosis. Because of its novel mode of action it does not show cross-resistance with conventional chemotherapeutic agents and has a very good side-effect profile. Published phase II data have demonstrated impressive activity in relapsed low-grade and follicular non-Hodgkin's lymphoma with an overall response rate in evaluable patients of 50%[12]. In an attempt to enhance cytotoxicity, monoclonal antibodies have been conjugated with both plant and bacterial toxins. Response rates as high as 30% have been observed in advanced, relapsed and refractory B-cell lymphomas. Future potential advances include the use of immunotoxin cocktails targeting several antigens simultaneously, the combination with other treatment modalities and the reduction of immunogenicity and non-specific toxicity of toxins. Another approach to the modification of monoclonal antibodies has been the addition of radionuclides. B-cell lymphomas are often exquisitely radiosensitive and the β-particles released are cytotoxic over several cell diameters, allowing the penetration of tumour nodules and cell kill of antibody negative mutants. The most commonly used radionuclides are ^{131}Iodine and ^{90}Yttrium, and the most successful conjugates have been radiolabelled CD20. Tositumomab is an example of a ^{131}Iodine-labelled anti-CD20 monoclonal antibody. The highest response rates have been observed in untreated B-cell malignancies, but responses have also been seen in relapsed, refractory and transformed disease[13,14]. Antisense oligonucleotides are chemically modified single strand DNA molecules with complementary nucleotide sequences to target mRNA, and have the potential to inhibit gene expression. One such target is the Bcl-2 gene, over-expression of which leads to cellular resistance to apoptosis and subsequent chemoresistance. Phase I data of Bcl-2 antisense are promising, with the majority of patients demonstrating a reduction in Bcl-2 protein, and a favourable toxicity profile[15].

Imaging

Imaging has a central role in the management of lymphoma, and advances continue to improve our knowledge of the natural history and biology of this disease. The accurate staging of lymphomas is vital if optimal therapy is to be delivered. One major improvement in the management of lymphomas has been the end of routine laparotomy and splenectomy in the staging of these patients. Although the routine use of systemic

chemotherapy has played a part, the advances in imaging, primarily CT scanning, have obviated the need for these procedures and the concomitant short- and long-term morbidity. Response assessment using conventional imaging techniques can be problematic. One common clinical issue is the interpretation of residual abnormalities following treatment. Series have reported the presence of radiological abnormalities following the end of therapy to be as high as 40%[16]. The majority of these abnormalities represent benign changes, including inflammatory and fibrotic tissue with as few as 10% of cases containing active disease[16]. Functional imaging techniques, such as FDG-PET, gallium scanning and MR, are increasingly being recognized as potential discriminators of disease activity, and their impact on the clinical management of lymphomas is already significant. A number of potential applications of FDG-PET are presently being investigated, including the grading of malignancies, the assessment of prognosis and the early assessment of treatment response, which could potentially allow tailored treatment in individual patients based on the biological characteristics of the tumour.

Conclusion

The management of lymphomas continues to improve with advances in treatment, including the development of novel therapies. The importance of a multidisciplinary approach cannot be underestimated and contributions from a number of disciplines including radiology, histopathology and immunology have added to our understanding of the disease and facilitated these therapeutic advances.

References

[1] Gall EA, Mallory TB. Malignant lymphoma. A clinicopathological survey of 618 cases. Am J Pathol 1942; 18: 381–429.

[2] Harris NL, Jaffe ES, Stein H *et al*. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84: 1361–92.

[3] Harris NL, Jaffe ES, Diebold J *et al*. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting — Airlie House, Virginia, November 1997. J Clin Oncol 1999; 17: 3835–49.

[4] A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993; 329: 987–94.

[5] Glick JH, Kim K, Earle J *et al*. An ECOG randomised phase III trial of CHOP vs CHOP + radiotherapy for intermediate grade early stage non-Hodgkin's lymphoma. Proc Am Soc Clin Oncol 1995; Abstr 1221.

[6] Miller TP, Dahlberg S, Cassady JR *et al*. Three cycles of CHOP plus radiotherapy is superior to eight cycles of CHOP alone for localized intermediate and high grade non-Hodgkin's lymphoma: a Southwest Oncology Group study. Proc Am Soc Clin Oncol 1996; Abstr 1257.

[7] Horning SJ, Williams J, Bartlett NL *et al*. Assessment of the Stanford V regimen and consolidative radiotherapy for bulky and advanced Hodgkin's disease: Eastern Cooperative Oncology Group pilot study E1492. J Clin Oncol 2000; 18: 972–80.

[8] Diehl V, Franklin J, Hasenclever D *et al*. BEACOPP, a new dose-escalated and accelerated regimen, is at least as effective as COPP/ABVD in patients with advanced-stage Hodgkin's lymphoma: interim report from a trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 1998; 16: 3810–21.

[9] Fisher RI, Gaynor ER, Dahlberg S *et al*. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328: 1002–6.

[10] Philip T, Guglielmi C, Hagenbeek A *et al*. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995; 333: 1540–5.

[11] Linch DC, Winfield D, Goldstone AH *et al*. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet 1993; 341: 1051–4.

[12] McLaughlin P, Grillo-Lopez AJ, Link BK *et al*. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998; 16: 2825–33.

[13] Kaminski MS, Estes J, Regan D *et al*. Front-line treatment of advanced B cell low-grade lymphoma (LGL) with radiolabelled anti-B1 antibody: Initial experience. Proc Am Soc Clin Oncol 1997.

[14] Vose JM, Wahl RL, Saleh M *et al*. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2000; 18: 1316–23.

[15] Waters JS, Webb A, Cunningham D *et al*. Phase I clinical and pharmacokinetic study of bcl-2 antisense oligonucleotide therapy in patients with non-Hodgkin's lymphoma. J Clin Oncol 2000; 18: 1812–23.

[16] Surbone A, Longo DL, DeVita VT Jr *et al*. Residual abdominal masses in aggressive non-Hodgkin's lymphoma after combination chemotherapy: significance and management. J Clin Oncol 1988; 6: 1832–7.

Intrathoracic lymphoma

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The staging and follow-up of Hodgkin's Disease (HD) and non-Hodgkin's lymphoma (NHL) depends on imaging. Intrathoracic involvement is more common in HD (75%) than in NHL (48%)[1]. The chest radiograph

remains the basic examination for evaluation of intrathoracic disease. It demonstrates moderate to extensive adenopathy readily but there is no question that CT is much more sensitive in demonstrating subtle disease.

Value of CT

CT of the thorax in Hodgkin's disease (HD) can change both the staging and the treatment of the disease[1–4]. The change is usually an upstaging due to identification of additional nodal groups or evidence of extranodal extension of disease outside the lymph nodes[1–3]. Less frequently CT will disprove the presence of suspected disease and thus alter therapy[1].

In the largest series dealing with the effect of CT on therapy in HD patients, treatment was altered in 9.4% (19 of 203) of patients[2]. The group in whom therapy was most frequently altered was of those patients receiving radiation therapy alone. Nine of 65 (13.8%) in this group had their treatment altered. In those receiving both chemotherapy and radiotherapy, therapy was altered in 10 of 122 (8.2%) patients. CT scans had no influence on the therapy decisions in those patients treated with chemotherapy alone.

Additionally 14 of 47 (30%) patients with 'normal' chest radiographs were found to have occult disease at CT. However, in only one of these 14 patients was treatment altered. This serves to make the distinction between new information and information that alters therapy.

CT of the thorax is recommended in all patients with HD who are to receive radiotherapy either alone or in combination with chemotherapy. CT of the chest has also been of benefit in staging of patients with (NHL)[3]. However, the NHLs are generally treated by chemotherapy and the detection of small foci of disease may be less critical than in HD. CT is, however, extremely valuable in establishing a baseline and the follow-up of patients with NHL.

With few exceptions magnetic resonance imaging (MR) has not demonstrated an advantage over CT in evaluating intrathoracic lymphoma. Chest wall and spinal involvement may be better evaluated with MR. MR has not been able to distinguish satisfactorily between viable and sterilized tumors. The role of positron emission tomography is not yet clear and is being evaluated.

Appearance

Mediastinum

All of the mediastinal nodal groups are usually more frequently involved in HD than NHL[1]. Typically, HD involves nodes by contiguity. The superior mediastinum is almost invariably involved before or in association with hilar or lower mediastinal disease. HD infrequently presents with bilateral hilar and right paratracheal adenopathy similar to sarcoidosis. Isolated hilar adenopathy is only rarely seen.

Intrathoracic disease of NHL may follow the patterns described for HD. However, contiguity of nodal disease typical for HD is frequently absent in NHL. Mediastinal masses of large B-cell lymphoma may mimic HD[5], but atypical intrathoracic presentations, particularly in other NHL, are not unusual.

Significant tracheobronchial compression by the nodes in HD is uncommon but can be seen with bulky disease. Bulky mediastinal disease is less common in patients with NHL. Primary bronchogenic carcinoma is more likely to cause tracheobronchial narrowing than HD. Superior vena cava syndrome and phrenic nerve paralysis are also more common in bronchogenic carcinoma than in HD.

Involvement of the paratracheal nodes and/or prevascular nodal groups is the most common thoracic lymph node manifestation and occurs in 66–82% of patients with HD[1,2,4]. These are followed by subcarinal nodes (24%), internal mammary nodes (21%), posterior mediastinal nodes (18%), anterior diaphragmatic nodes (14%) and hilar nodes (11%)[1]. Any node >1.0 cm in transverse diameter was considered abnormal[2]. Unfortunately, there are no absolute size measurements available for any mediastinal nodal groups. There is usually no question of nodal involvement when the adenopathy is bulky, but this determination can be an extremely difficult question for paratracheal, tracheobronchial angle, prevascular and subcarinal nodes in the 1 to 2 cm range.

Subtle changes in the left prevascular region may be appreciated on the conventional radiograph by obscuration of all or part of the aortic knob on the P-A projection. A convex bulge into the lung at the junction of the descending aorta and the left pulmonary artery is also an indication of prevascular adenopathy[6]. The area may be concave or straight, but should not have a convex bulge.

The identification of subtle right tracheobronchial and right paratracheal adenopathy may be quite difficult. Using various criteria with chest radiographs, adenopathy could only be identified in 89% of patients who had nodes >15 mm[7]. The increased sensitivity of CT is evident.

In Castellino's series[2], only 7% of patients with HD had adenopathy in the paratracheal/prevascular areas identified with CT alone. In 77% the disease was evident with both CT and chest radiographs. In our series, 19% more patients had paratracheal/prevascular adenopathy seen only at CT[1].

Subcarinal adenopathy is often most difficult to identity of the more frequently involved nodal groups, unless the disease is extensive[8]. CT is far more helpful.

Internal mammary adenopathy is not usually seen in frontal chest radiographs unless bulky and is more frequently seen in the lateral view immediately behind the sternum. Even in the lateral view, internal mammary nodes are not identifiable unless moderately enlarged. At CT we consider the node enlarged when it is larger than the accompanying vessels.

Anterior diaphragmatic adenopathy is also more frequently seen with CT than on conventional studies. The paracardiac nodes (the medial component of the anterior diaphragmatic group) when significantly enlarged are seen as masses in the cardiophrenic angles[10]. The more lateral anterior diaphragmatic nodes are rarely seen except with CT. The identification of anterior diaphragmatic nodes suggests that they are enlarged. Identification of these nodes is particularly important in patients to be treated with radiation therapy. These nodes might otherwise be excluded from the radiation portals in order to spare the heart. The nodes are a not uncommon site of recurrence[9].

The posterior mediastinal nodes include the paraspinous nodes, the periesophageal and periaortic nodes. These are much more frequently seen at CT[1–3]. Identification of nodes in this area speaks for their enlargement.

Thymic enlargement is not uncommon in HD and has been found in 30% of patients with intrathoracic disease at presentation[10]. Identifying thymic enlargement is easier with CT than with conventional chest radiographs. Following therapy, residual enlargement can be the result of recurrent disease, thymic rebound, or the development or persistence of thymic cysts[11].

Lung

Pulmonary parenchymal involvement in HD is almost always associated with hilar and/or mediastinal nodal disease. In a review by Kaplan[12] of 340 consecutive previously untreated patients, there were 'no cases in which HD has been confined to the parenchyma of the lung without associated hilar and mediastinal adenopathy'.

In a series of 100 and 203 patients with HD investigated at presentation with CT, 8% had pulmonary involvement and all had hilar and/or mediastinal nodal disease[1,2]. Only one case of parenchymal involvement was not seen with chest radiography. CT scans, in some cases, showed more extensive parenchymal disease. CT will occasionally identify hilar and/or pulmonary parenchymal disease extending from the hili obscured by bulky mediastinal mass.

In the untreated patient with HD, a lung lesion without mediastinal disease should be evaluated for a second process. In the treated patient, relapse in the chest is commonly seen in the lungs. With recurrent disease, pulmonary involvement without nodal disease is more common than it is at presentation. Primary pulmonary parenchymal lymphoma is rare.

In NHL, pulmonary or pleural lesions may be seen without mediastinal or hilar adenopathy. In our series, parenchymal involvement of NHL was more frequently seen only at CT. The bronchovascular bundle is the area most frequently involved[13]. Radiographically ill-defined densities following the bronchovascular bundles are seen. End on, the involvement appears as nodules while in profile it appears more linear. Discrete nodules can also be seen. They may be less well defined than typical pulmonary metastasis and can be seen in both HD and NHL as a stage IV manifestation in an untreated patient or as an indicator of relapse. Cavitation may occur.

The appearance of pulmonary lymphomas also includes consolidation and atelectasis of a lobe or segment, due to bronchial compression by nodes or endobronchial disease. If the lung clears and is reaerated within a few days of initiation of therapy, the findings were probably due to atelectasis. Actual invasion of the lung requires longer to clear, and usually leaves some residual scarring and loss of volume. Air-bronchograms may be present due to masses around the patent bronchi.

The least common parenchymal manifestation of the lymphomas is an interstitial pattern which represents disease along the peripheral lymphatics. This is so uncommon, particularly in HD, that other causes for the radiographic appearance should be excluded.

Pleura and pericardium

In both ours and Castellino's experience, pleural effusions were more common in NHL than HD[1–3]. However, at CT it is not unusual to see small amounts of fluid in patients with HD, especially in those with large mediastinal masses. The effusions clear promptly with therapy and are thought to be benign and related to lymphatic and/or venous obstruction.

Solid pleural involvement at autopsy (26%)[16] and 30% in a group of patients with advanced or recurrent disease[14] has also been reported. It is far less frequent at presentation. It may occur anywhere along the pleural surface and is frequently accompanied by fluid. It may appear as plaques, as discrete nodules, or both in conjunction with other pulmonary parenchymal involvement or alone. Rarely, solid pleural involvement may be the sole manifestation of recurrent disease[15].

Pericardial effusion may be seen in patients with lymphoma, particularly those with HD with large mediastinal masses. These usually resolve quickly following institution of therapy.

Chest wall

Chest wall involvement of Hodgkin's disease is not uncommon. It may be either an initial manifestation of the disease or of recurrence[16].

The most common type of chest wall involvement in HD is direct extension from anterior mediastinal disease with internal mammary node involvement. Occasionally, masses are seen beneath or between the pectoral muscles without contiguous mediastinal or axillary adenopathy. Direct invasion may occur in association with pleural masses. Soft tissue presentation without intrathoracic adenopathy may occur and is more common in NHL, particularly large cell lymphoma.

References

[1] Romano, Libshitz HI. Hodgkin disease and non-Hodgkin lymphoma: plain chest radiographs and chest computed tomography of thoracic involvement in previously untreated patients. Radiol Med 1988; 95: 49–53.

[2] Castellino RA, Blank N, Hoppe RT *et al.* Hodgkin disease: contributions of chest CT in the initial staging evaluation. Radiology 1986; 160: 603–5.

[3] Castellino RA, Hilton S, O'Brien JP *et al.* Non-Hodgkin lymphoma: contribution of chest CT on the initial staging evaluation. Radiology 1996; 9: 129–32.

[4] Diehl LF, Hopper KD, Gigveri J *et al.* The pattern of intrathoracic Hodgkin's disease assessed by computed tomography. J Clin Oncol 1991; 9: 438–43.

[5] Shaffer K, Smith D, Kim D *et al.* Primary mediastinal large B-cell lymphoma: radiologic findings at presentation.

[6] Blank N, Castellino RA. Patterns of pleural reflections of the left superior mediastinum. Radiology 1972; 102: 585–9.

[7] Müller NL, Webb WR, Gamsu G. Paratracheal lymphadenopathy: radiographic findings and correlation with CT. Radiology 1985; 156: 761–5.

[8] Müller NL, Webb WR, Gamsu G. Subcarinal lymph node enlargement: radiographic findings and CT correlation. Am J Radiol 1985; 145: 15–9.

[9] Meyer KE, McLoud TC, Lindfors KK. CT demonstration of cardiophrenic angle lymphadenopathy in Hodgkin disease. J Comput Assist Tomogr 1985; 9: 485–8.

[10] Heron CW, Husband JE, Williams MP. Hodgkin disease: CT of the thymus. Radiology 1988; 167: 647–51.

[11] Lindfors KK, Meyer JE, Dedrick CG *et al.* Thymic cysts in mediastinal Hodgkin disease. Radiology 1985; 156: 37–41.

[12] Kaplan HS. Contiguity and progression in Hodgkin's disease. Cancer Research 1971; 31: 1811–3.

[13] Stolberg HO, Patt NL, MacEwen KF *et al.* Hodgkin's disease of the lung: roentgenologic-pathologic correlation. 1964; 92: 96–115.

[14] Shuman LS, Libshitz HI. Solid pleural manifestations of lymphoma. Am J Radiol 1984; 142: 269–73.

[15] Bramson RT, Mikhael MA, Sagel SS *et al.* Recurrent Hodgkin's disease manifesting roentgenographically as a pleural mass. Chest 1974; 66: 89–91.

[16] Cho CS, Blank N, Castellino RA. Computerized tomography evaluation of chest wall involvement in lymphoma. Cancer 1985; 55: 1892–4.

Extranodal manifestations of lymphoma in the abdomen

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Introduction

Involvement of extranodal sites by lymphoma usually occurs in the presence of widespread disease elsewhere. Such secondary involvement occurs in both Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). However, in approximately 30–40% of cases, primary involvement of an extranodal site occurs with lymph node involvement limited to the regional group of nodes — Stage 1-IIE. Both primary and secondary extranodal involvement is more common in NHL than HD. As primary extranodal HD is extremely rare, rigorous exclusion of disease elsewhere is essential before this diagnosis can be made. The incidence of extranodal involvement in NHL depends on a number of factors including the age of the patient, the presence of pre-existing immunodeficiency and the pathological subtype of lymphoma. For example, in children, lymphomas are more likely to arise extranodally, especially in the gastrointestinal tract, the major abdominal viscera and extranodal locations in the head and neck[1,2]. In the immunocompromised host, lymphomas also tend to occur at extranodal sites. In both these patient groups, the high incidence of extranodal involvement is a reflection of the fact that such lymphomas are usually of the more aggressive histological subtypes. As the frequency of NHL is increasing (both in the general population and in the immunocompromised), the incidence of extranodal disease is rising faster than that of nodal disease[3]. For example, primary lymphomas of the CNS and orbit are increasing in frequency at a rate of 10% and 6%, respectively, per annum.

Of the various pathological forms of NHL, mantle cell (a diffuse low-grade B cell lymphoma), lymphoblastic lymphomas (80% of which are T cell), Burkitt's (small cell non-cleaved) and lymphomas arising in mucosal-associated lymphoid tissue (MALT lymphomas) demonstrate a propensity to arise in extranodal sites.

Classification

The classification of NHL has taxed pathologists and physicians alike. It is salutary to note that in the published literature there have been four attempts at classifying HD and over 40 attempts at classifying NHL in the last 50 years. Many of the difficulties that beset early taxonomists have been overcome with improved immunological and molecular methods of diagnosis.

This culminated in the emergence of a new classification scheme, the Revised European-American Lymphoma classification (REAL), that depends heavily on a triad of morphology, immunophenotype and molecular methods for defining disease entities. The scheme forms the backbone of the forthcoming 2nd WHO Classification of Haematological Malignancies. For the purposes of this review, the REAL scheme will be adopted as the finalized WHO classification is presently unavailable. The REAL classification is an exhaustive statement about lymphoma and many rare conditions are included within it. Thus, an indication of the relative frequencies of each of the lymphoma types is given for an European/North American population.

Prognostic factors

It has long been evident that prognosis varies between patients and between subtypes of lymphoma. In order to evaluate therapies better and indeed to choose the most appropriate treatment for a given patient, it was considered imperative that a uniform prognostic system be established. Thus, the International Prognostic Index (IPI) was developed following analysis of clinical features of over 3000 patients with 'aggressive' histology NHL. Five factors were statistically associated with significantly inferior overall survival:

age >60 years
elevated serum LDH
ECOG performance stages >1 (i.e. non-ambulatory), advanced stage 3 or 4
presence of >1 extranodal site of disease. Thus the detection of extranodal disease is extremely important.

Hepatobiliary system and spleen

Liver

Liver involvement is present in up to 15% of adult patients with NHL (more frequently in children with NHL) and in about 5% of patients with HD, at the time of presentation. In HD, liver involvement almost invariably occurs in association with splenic disease. True primary hepatic lymphoma is extremely rare, up to 25% of affected patients are HBsAg-positive and there is also an increased incidence of chronic active hepatitis.

Pathologically, diffuse infiltration is the most common form of involvement as focal areas of infiltration are only present in 5–10% of patients with liver lymphoma. Therefore, cross-sectional imaging is insensitive in the detection of liver involvement. However, hepatomegaly strongly suggests the presence of diffuse infiltration (in contradistinction to the significance of splenomegaly). Despite initial enthusiasm, MRI has been shown to be relatively insensitive in the detection of diffuse disease[4–6]. The focal form of infiltration results in miliary nodules or large solitary or multiple masses resembling metastases on cross-sectional imaging. On ultrasound they are usually well-defined and hypoechoic; on CT they are hypodense before and after intravenous injection of contrast medium; on MR they are of higher signal intensity than the surrounding normal parenchyma on T2-weighted sequences[7].

NHL of the bile ducts and gall bladder is rare but occurs with relatively high frequency in patients with ARL.

Spleen

The spleen is involved in 40% of patients with HD at the time of presentation, usually in the presence of nodal disease above and below the diaphragm (Stage III), but in a small proportion it is the sole focus of intra-abdominal disease. In the majority of patients, the involvement is diffuse and particularly difficult to identify on cross-sectional imaging because splenomegaly does not necessarily indicate involvement; 33% of patients have splenomegaly without infiltration and, conversely, 33% of normal-sized spleens are found to contain tumour following splenectomy[8].

Focal splenic deposits occur in only about 10–25% of cases which, when they are greater than 1 cm in diameter, can be demonstrated on any form of cross-sectional imaging.

The sensitivity of ultrasound and CT for the detection of splenic involvement has proved to be extremely low (about 35%). MRI with supraparamagnetic ion oxide may improve the diagnostic accuracy but is seldom undertaken to assess the splenic status[9]. In the past, the poor sensitivity of imaging for the detection of splenic disease necessitated staging laparotomy with splenectomy. However, the development of effective combination chemotherapy with good salvage regimens has led to the abandonment of this practice almost universally.

Primary splenic NHL is rare, accounting for 1% of all patients who present with splenomegaly. Splenic involvement is also a particular feature of certain other pathological subtypes of NHL such as mantle cell lymphoma and splenic marginal zone lymphoma.

Gastrointestinal tract

The gastrointestinal tract is the initial site of lymphomatous involvement in up to 10% of all adult patients and up to 30% of children. It is therefore the most common site of primary extranodal NHL accounting for 30–45% of all extranodal presentations[7]. It is particularly common in children. As elsewhere, primary HD of the gastrointestinal tract is most unusual. Secondary involvement of the gastrointestinal tract is extremely common, usually from direct extension from involved mesenteric or retroperitoneal lymph nodes and consequently multiple sites of involvement do occur.

Primary lymphomas arise from lymphoid tissue of the lamina propria and the submucosa of the bowel wall,

and occur most frequently below the age of 10 years and in the 6th decade. Primary gastrointestinal lymphoma is usually unifocal and accepted criteria for the diagnosis of primary disease include:

an absence of superficial or intrathoracic lymph node enlargement
no involvement of the liver or spleen
a normal white cell count
no more than local regional lymph node enlargement

A modified Ann Arbor classification can be applied:

Stage I indicating involvement of the hollow visceral wall alone (substaged according to bulk and extent of tumour)
Stage II indicating local extension, either to adjacent organs (IIE) or to draining lymph nodes (local first echelon or region).

Stomach

Involvement of the stomach accounts for about 50% of all gastrointestinal lymphoma being affected both in the primary and secondary forms.

Primary lymphoma accounts for about 2–5% of all gastric tumours[10]. It originates in the submucosa affecting the antrum more commonly than the body and the cardia. Radiologically, the appearances reflect the gross pathological findings; common appearances are multiple nodules, some with central ulceration, or a large, fungating lesion with or without ulceration. About a third of patients have diffuse infiltration with marked thickening of the wall and narrowing of the lumen, sometimes with extension into the duodenum indistinguishable from linitis plastica. Only about 10% are characterized by diffuse enlargement of the gastric folds, similar to the pattern seen in hypertrophic gastritis.

As the disease originates in the submucosa, the signs described above are best demonstrated on barium studies or endoscopically, but these investigations do not reflect the true extent of the disease. Computed tomography has proved particularly valuable in showing extensive gastric wall thickening and the extent of the extraluminal mass. A characteristic feature of gastric lymphoma is that there is rarely infiltration of adjacent organs, unlike in gastric carcinoma[11]. In the MALT lymphomas the gastric wall thickening may be minimal and CT is then of limited value in staging and assessment of response.

Small bowel

Lymphoma accounts for up to 50% of all primary tumours of the small bowel, occurring most frequently in the terminal ileum and becoming progressively less frequent proximally, such that duodenal lymphomas are rare[12]. The disease is multifocal in up to 50% of cases and because the disease originates in the lymphoid follicles, mural thickening with constriction of segments of bowel is typical. Patients commonly present with obstructive symptoms. The thickening of bowel is well demonstrated on CT. With progressive tumour spread through the submucosa and muscularis mucosa, long tube-like segments result. Aneurysmal dilatation of long segments of bowel also develop, presumably due to infiltration of the autonomic plexus. Such alternating areas of dilatation and constriction are a common manifestation of small bowel infiltration[12].

Occasionally, the lymphomatous infiltration is predominantly submucosal, which results in multiple nodules or polyps of varying size scattered throughout the small bowel, but predominantly in the terminal ileum. It is this form of lymphoma that typically results in intussusception, usually in the ileocaecal region. This is the most common cause of intussusception in children older than 6 years. Barium studies typically show multiple polypoid filling defects, with or without central ulceration, and irregular thickening of the valvulae.

Secondary invasion of the small bowel is commonly seen when large mesenteric lymph node masses cause displacement encasement or compression of the bowel. Enteropathy-associated T-cell lymphoma and immunoproliferative small intestinal disease (alpha-chain disease) commonly present with clinical and imaging features of malabsorption. The latter is particularly likely to affect the whole small intestine, especially the duodenum and jejunum.

Colon and rectum

Primary colonic lymphomas are usually of the Burkitt's or MALT subtypes, but account for under 0.1% of all colonic neoplasms, most arising in the caecum and rectum. Patients usually present with obstruction and rectal bleeding. The most common pattern of the disease is a diffuse or segmental distribution of small nodules 0.2 to 2.0 cm in diameter, typically with the mucosa intact. As the disease progresses, fissures, ulceration, structures and even fistulae can develop. A less common form of the disease is the solitary polypoid mass, often in the caecum, indistinguishable from carcinoma on imaging unless there is concomitant involvement of the terminal ileum, which is more suggestive of lymphoma.

In very advanced disease, there may be marked thickening of the colonic or rectal folds resulting in focal strictures or ulcerative masses with fistula formation. In the rectosigmoid, lymphomatous strictures are generally longer than carcinomatous ones and irregular excavation of the mass strongly suggests lymphoma.

Oesophagus

Involvement of the oesaphagus is extremely unusual and begins as a submucosal lesion, usually in the distal third of the oesophagus resulting in smooth luminal narrowing with intact overlying mucosa. Later, ulceration can develop. Secondary involvement by contiguous spread

from adjacent nodal disease is more common but rarely results in dysphagia.

Pancreas

Primary pancreatic lymphoma accounts for only 1.3% of all pancreatic malignancies[13]. Intrinsic involvement of the pancreas usually results in a solitary mass lesion, indistinguishable from primary adenocarcinoma on ultrasound, CT or MRI[14]. Less commonly, diffuse uniform enlargement of the pancreas is seen. As elsewhere, involvement is far more common in NHL than in HD.

Secondary pancreatic involvement is seen in association with disease elsewhere and is most likely to result from direct infiltration from adjacent nodal masses.

Genitourinary tract

Although the genitourinary tract is uncommonly involved at the time of presentation (<5%), more than 50% of patients will have involvement of some part of the genitourinary tract in endstage disease. The testicle is the most commonly involved organ followed by the kidney and the perirenal space; only rarely are the bladder, prostate, uterus, vagina or ovaries involved[15]. True primary genitourinary lymphoma is rare as there is normally very little lymphoid tissue within the genitourinary tract.

Despite the sensitivity of CT in detecting lymphomatous renal masses, a large discrepancy exists between the frequency of involvement diagnosed ante mortem and post mortem, probably explained by the fact that renal involvement is a late phenomenon. Detection of renal involvement is usually of limited clinical importance as it rarely alters the stage of the disease, close to 90% of cases are in association with high-grade NHL, in more than 40% of patients the disease occurs at the time of recurrence only, and renal function is usually normal[16].

On imaging, the most common disease pattern is multiple masses, which result from haematogenous spread of lymphomatous cells (usually diffuse, large cell types but also non-cleaved cells of the Burkitt's type) entering the kidney. On ultrasound these masses are hypoechoic with little posterior acoustic enhancement[17,18]. On CT, the masses may show a typical 'density reversal pattern' before and after contrast administration with the lesion being more dense than the surrounding parenchyma before contrast medium administration and less dense after. There may be associated soft tissue stranding in the perirenal space. A solitary renal mass is seen in only 5–15% of cases and may be indistinguishable from renal cell carcinoma[16]. An important feature of renal masses occurring in NHL is that in over 50% of cases there is no evidence of retroperitoneal lymph node enlargement detectable on CT.

Direct infiltration of the kidney by contiguous retroperitoneal nodal masses is the second most common type of renal involvement, accounting for about 25% of cases. There is often associated encasement of the renal vessels and also extension into the renal hilum and sinus. In a further 10%, soft tissue mass can be seen in the perirenal space, occasionally encasing the kidney without any evidence of invasion of the parenchyma.

Diffuse intrinsic infiltration of the kidney resulting in global enlargement is the least common manifestation of renal lymphomatous involvement. On ultrasound, the kidneys are diffusely enlarged, appearing diffusely hypoechoic. On CT, the appearance following intravenous injection of contrast medium is variable, but usually the normal parenchymal enhancement is replaced by homogeneous non-enhancing tissue.

Bladder and prostate

Bladder

The urinary bladder is a rare site of primary extranodal involvement, accounting for less than 1% of all bladder tumours[18]. It occurs more frequently in women than in men and there is often a history of recurrent cystitis. Small cell and MALT types are seen, both characteristically producing large multilobular submucosal masses with minimal or no mucosal ulceration. Transmural spread into adjacent pelvic organs can occur, as well demonstrated on cross-sectional imaging[19]. The prognosis is generally good.

Secondary lymphoma of the bladder is more common than primary disease and is found in 10–15% of patients with lymphoma at autopsy[15,19]. Such secondary involvement can affect the wall of the bladder intrinsically or result from contiguous spread from the adjacent involved nodes. Microscopic involvement is far more common than gross infiltration, but this too can be associated with haematuria. On CT the appearances are usually non-specific, indistinguishable from transitional cell carcinoma, producing either diffuse widespread thickening of the bladder wall or a large nodular mass.

Prostate

Primary prostatic lymphoma is also extremely rare, but in contradistinction to primary bladder NHL it carries a very poor prognosis. It is usually intermediate to high-grade and produces irritative obstructive symptoms. Histological examination usually shows diffuse infiltration with spread into the periprostatic tissues. Solitary nodules are uncommon. Most frequently, prostatic involvement is secondary to spread from the adjacent nodes.

Adrenal glands

Primary adrenal lymphoma is extremely rare, usually occurring in men over the age of 60. Secondary involvement of the adrenals is detected in about 6% of patients

undergoing routine abdominal staging CT, usually in the presence of widespread retroperitoneal disease. Adrenal insufficiency is most unusual, even in the presence of bilateral disease. The appearance on cross-sectional imaging is indistinguishable from that of metastases. Bilateral adrenal hyperplasia in the absence of metastatic involvement has also been described[20].

Testis

Testicular lymphoma accounts for about 5% of primary testicular tumours overall: 25–50% of those in patients over 50 years and it is the most common primary tumour over the age of 60 years[21]. It is vanishingly rare in HD but is seen at presentation in approximately 1% of all patients with NHL, usually of intermediate to high-grade, diffuse large cell and Burkitt's type. There is an association with lymphoma of Waldeyer's ring, the skin and central nervous system. Patients usually present with a painless testicular swelling and in up to 25% of cases the involvement is bilateral.

Ultrasonically, the lesions usually have a non-specific appearance; with focal areas of decreased echogenicity. A more diffuse decrease in reflectivity of the testicle (without any focal abnormality) is also a well-recognized pattern. At present, MR does not appear to have advantage over ultrasound in the detection of testicular involvement[22].

Because of the association with disease elsewhere, staging must always include ultrasonic evaluation of the contralateral testis and whole body CT. Cranial CT or MRI and CSF examination should also be considered. Relapse can also occur in the contralateral testis.

Female genital tract

Isolated lymphomatous involvement of the female genital organs is rare, accounting for approximately 1% of extranodal NHL. Nearly 75% of women affected are post-menopausal and present with vaginal bleeding[23,24]. It affects the cervix more frequently than the uterus and vagina. Involvement of these gynaecological organs is best demonstrated by MRI where primary lymphoma of the cervix and/or vagina is characterized by a large soft tissue mass best seen as high signal intensity lesions on T2-weighting and clearly distinguished from the surrounding normal tissues[25]. Involvement of the uterine body usually produces diffuse enlargement, often with a lobular contour similar to a fibroid. Primary uterine lymphoma has a good prognosis and MRI can demonstrate complete resolution.

Primary ovarian lymphoma, by contrast, has a very poor prognosis as it often presents late and disease is frequently bilateral. It is less common than uterine lymphoma. In young women disease is usually of the high-grade lymphoblastic type, whereas in older women intermediate grade Burkitt's-like tumours are seen with greater frequency[26]. Imaging appearances are identical to those of ovarian carcinoma[27].

References

[1] Murphy S. Childhood non-Hodgkin's lymphoma. N Engl J Med 1978; 299: 1446–8.

[2] Ng YY, Healy JC, Vincent JM, Kingston JE, Armstrong P, Reznek RH. The radiology of non-Hodgkin's lymphoma in childhood: a review of 80 cases. Clin Radiol 1994; 49: 594–600.

[3] Devesa SS, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. Cancer Res 1992; 52: 5432s.

[4] Weinreb JC, Brateman L, Maravilla KR. Magnetic resonance imaging of hepatic lymphoma. Am J Roentgenol 1984; 143: 1211–4.

[5] Nyman RS, Rhen SM, Ericsson A *et al*. An attempt to characterise malignant lymphoma in spleen, liver and lymph nodes with magnetic resonance imaging. Acta Radiol 1987; 28: 527–33.

[6] Richards MA, Webb JAW, Reznek RH *et al*. Detection of spread of malignant lymphoma to the liver at low field strength magnetic resonance imaging. Br Med J 1986; 293: 1126–8.

[7] Weissleder R, Stark DD, Elizondo G *et al*. MRI of hepatic lymphoma. Magn Reson Imag 1988; 6: 675–81.

[8] Castellino RA, Marglin S, Blank N. Hodgkin disease, the non-Hodgkin lymphomas and the leukaemias in the retroperitoneum. Semin Roentgenol 1980; 15: 288–301.

[9] Weissleder R, Elizondo G, Stark DD *et al*. The diagnosis of splenic lymphoma by MR imaging: value of superparamagnetic iron oxide. Am J Roentenol 1989; 152: 175–80.

[10] Brady LW, Asbell SO. Malignant lymphoma of the gastrointestinal tract. Radiology 1980; 137: 291–8.

[11] Megibow AJ, Balthazar EJ, Naidich DP, Bosniak MA. Computed tomography of gastrointestinal lymphoma. Am J Roentgenol 1983; 141: 541–3.

[12] Dodd GD. Lymphoma of the hollow abdominal viscera. Radiol Clin N Am 1990; 28: 771–83.

[13] Reed K, Vose PC, Jarstfer BS. Pancreatic cancer: 30 year review (1947 to 1977). Am J Surg 1979; 138: 929–33.

[14] Shirkhoda A, Ros PR, Farah J, Staab E. Lymphoma of the solid abdominal viscera. Radiol Clin N Am 1990; 28: 785–99.

[15] Charnsangavej C. Lymphoma of the genitourinary tract. Radiol Clin N Am 1990; 28: 865–77.

[16] Reznek RH, Mootoosamy I, Webb JAW, Richards MA. CT in renal and perirenal lymphoma: a further look. Clin Radiol 1990; 42: 233–8.

[17] Cohan RH, Dunnick NR, Leder RA, Baker ME. Computed tomography of renal lymphoma. J Comput Ass Tomogr 1990; 14: 933–8.

[18] Bailey JE, Roubidoux MA, Dunnick NR. Secondary renal neoplasms. Abdominal Imag 1998; 23: 266–74.

[19] Aigen AB, Phillips M. Primary malignant lymphoma of the urinary bladder. Urology 1986; 28: 235–7.

[20] Vincent JM, Morrison ID, Armstrong P, Reznek RH. Non-metastatic enlargement of the adrenal glands in patients with malignant disease. Clin Radiol 1994; 49: 456–60.

[21] Mostofi FK. Testicular tumors: epidemiologic, etiologic and pathologic features. Cancer 1973; 32: 1186–201.

[22] Thurnher S, Hricak H, Carroll PR, Pobiel RS, Filly RA. Imaging the testis: comparison between MR imaging and US. Radiology 1988; 167: 631–6.

[23] Harris NL, Scully RE. Malignant lymphoma and granulocytic sarcoma of the uterus and vagina. A clinicopathologic analysis of 27 cases. Cancer 1984; 53: 2530.

[24] Muntz HG, Ferry JA, Flynn D, Fuller AF, Tarraza HM. Stage IE primary malignant lymphomas of the uterine cervix. Cancer 1991; 68: 2023–32.
[25] Jenkins N, Husband J, Sellars N *et al*. MRI in primary non-Hodgkin's lymphoma of the vagina associated with a uterine congenital anomaly: a case report. Br J Radiol 1997; 70: 219–22.
[26] Monterroso V, Jaffe ES, Merino MJ, Medeiros LJ. Malignant lymphomas involving the ovary: a clinicopathological analysis of 39 cases. Am J Surg Pathol 1993; 17: 154.
[27] Glazer HS, Lee JS, Balfe DM, Mauro MA, Griffith R, Sagel SS. Non-Hodgkin lymphoma: computed tomographic demonstration of unusual extranodal involvement. Radiology 1983; 149: 211–7.

Lymphoma: residual masses

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Introduction

The assessment of the response of lymphoma to treatment may be difficult. CT is used in most institutions but cannot differentiate residual masses consisting of fibrosis from those that contain small foci of disease or identify which patients are likely to relapse. MRI offers some additional information, and functional imaging including the use of Gallium^{67} and positron emission tomography will have a role to play as will biopsy, either percutaneous or open.

CT and MRI

The assessment of lymphadenopathy on CT and MRI is based on size. Size criteria depend on the anatomical site but a short axis of 10 mm is used as a practical upper limit in the chest and abdomen. CT cannot differentiate enlarged reactive nodes from large involved nodes or identify micro-metastases in small nodes. In MRI the size criteria are used as for CT and the same problems exist. The use of super-paramagnetic iron oxide as a contrast agent may be helpful[1].

Monitoring change on CT

After treatment the nodal mass will decrease in size but the node will still be present. The accuracy of measurements using CT and MRI will depend partly on the tumour shape and site. CT does appear to be an accurate method of defining tumour volume in regular-shaped tumours, but irregular shaped tumours are more difficult to assess.

Tumour shrinkage usually indicates response to treatment[2], but as the node shrinks there may be fibrosis, necrosis or inflammation and the node may remain enlarged but disease free[3]. On CT, tumours are usually of soft tissue attenuation and may demonstrate areas of low attenuation, which indicate cystic degeneration or calcification in response to therapy. Nodules of viable tumour may remain undetected.

Monitoring change on MRI

MR, with its superior contrast resolution and changes in relaxation values, may help differentiate active tumour and necrosis[4]. On MRI most tumours are of low signal on T1W sequences and intermediate to high signal on T2W sequences. Signal intensity changes in response to therapy occur, with a reduction of signal intensity on T2W, which may be a reflection of fibrosis[5], although foci of persistent tumour can remain within the low signal area[6]. Dynamic contrast-enhanced MRI with gadolinium DTPA may add further information but the combination of functional imaging with CT or MRI is likely to be more helpful.

Radionuclide imaging

Functional imaging is provided by the use of Gallium^{67} and more recently positron emission tomography.

Gallium^{67}

Gallium (^{67}Ga) scintigraphy is used to restage after treatment, to evaluate residual masses, as a prognostic index, to detect recurrence after clinical remission and as an early predictor of chemotherapy response[7,8]. A baseline scan before treatment is considered essential, both to act as a comparison for post-therapy and also to identify the small number of lymphomas which are not gallium avid. A potential pitfall is that recent chemotherapy or radiotherapy may significantly reduce ^{67}Ga uptake into tumour cells that are still viable.

^{67}Ga scintigraphy has the advantage of whole body imaging, so disease recurrence distant from the primary site may be detected.

Positron emission tomography

^{18}F-fluorodeoxyglucose (^{18}FDG) PET is a realistic alternative to other imaging modalities. Positron emission tomography (PET), like other functional imaging techniques, can map functional/metabolic activity before structural changes have taken place. Tumours show enhanced glycolytic activity when compared with other tissue and lymphoma almost always displays avid uptake of ^{18}FDG, making PET scanning a very sensitive technique[9–11]. There is evidence that the degree of ^{18}FDG uptake is related to tumour grade and some of the very low-grade tumours, e.g. mucosa-associated lymphoid tissue (MALT) lymphoma, may not be suitable for this imaging modality.

In comparing ^{18}FDG PET to CT in the post-treatment evaluation of patients it has been shown that PET has a higher specificity, accuracy and positive predictive value[12]. The greater specificity of PET is largely due to the ability to detect viable tumour tissue within residual masses.

Residual masses

Residual masses on CT or MRI following treatment for lymphoma are a problem. They usually represent post-therapy fibrosis and commonly occur in up to 85% of patients treated for Hodgkin's Disease (HD), usually within the mediastinum and 40% of NHL[2,13–17]. Although these masses usually represent fibrosis, viable tissue may still be present. CT is unreliable in differentiating tumour from fibrosis as it relies on size, which is an insensitive measure, as the rate of decrease in size depends on the size and location of the original mass, the histology and treatment undertaken[18,19]. Tumours which initially contain a lot of fibrosis, for example nodular sclerosing HD, tend to decrease less in size in response to treatment than very cellular tumours and residual masses are more common.

Residual masses in the chest

The chest is frequently involved in HD and the thymus is a common site of involvement, occurring in up to 38% of adult and 27% of paediatric patients. Using CT, thymic size usually decreases within 3 months of treatment, although regression in size may continue over the next 11 months[18,20]. In the paediatric population mediastinal widening is usually an indication of fibrosis, but thymic re-growth by up to 50%, after chemotherapy is not uncommon. This thymic hyperplasia occurs in about 17% of children and it may be difficult to differentiate the hyperplastic from the thymus infiltrated with tumour. Neither CT nor MR is reliable in these cases, although the hyperplastic thymus is usually triangular whereas the infiltrated thymus is quadrilateral with a lobulated border[21]. Gallium or thallium studies may also be helpful in identifying active disease[22].

In adults, thymic hyperplasia following chemotherapy is less common than in children although it does occur, usually several months after treatment has ended. Hyperplasia should be considered the cause of thymic enlargement[23,24], rather than tumour infiltration, particularly if the thymus was not the original site of involvement and if there is no disease recurrence elsewhere. On MRI, treated thymic lymphoma is of low signal irrespective of thymic size. Relapse tends to occur in the large volume residual thymic masses, which are of heterogeneous signal intensity on T2W sequences, and these lesions need careful follow-up[22].

Thymic cysts may occur in Hodgkin's either at initial presentation (21–50%) or following radiotherapy. These cysts may persist or enlarge and this does not indicate residual or recurrent disease or an increased risk of relapse[16]. If haemorrhage occurs the thymus may undergo calcification. The presence of cystic change has no prognostic significance but does lead to a heterogeneous signal on MRI, which may be misleading.

On MRI, low signal within lymphomatous masses reflects fibrosis and a reduction in signal intensity after treatment suggests an increase in the percentage of residual fibrosis. Foci of tumour may, however, be found within the fibrosis and areas of high signal indicate oedema, necrosis or tumour[19]. It has been shown experimentally and in clinical practice that ^{67}Ga uptake correlates well with the presence of viable tumour[7,8]. A negative gallium scan is a good indicator for the absence of disease. False positives may occur in the presence of thymic hyperplasia[22].

Residual masses in the abdomen

In the abdomen, up to 40% of patients with NHL will have residual masses at the end of therapy but be in apparent clinical remission. This is a particular problem with large cell NHL, where 30–50% of patients presenting with a large intra-abdominal mass will have a residual mass after therapy[2,16]. This is more likely if there is bulky disease initially and large masses may also be more likely to recur. CT attenuation values cannot be used to differentiate fibrosis from residual disease, as they may be similar and biopsy may be required to differentiate residual masses from active disease. Percutaneous guided biopsy can be used in this group of patients[25] to avoid laparotomy although the presence of fibrosis leading to inadequate biopsies and sampling errors may be a problem. Surbone[2] reviewed 72 patients with abdominal masses at presentation; 40% had detectable residual masses after treatment. Twenty-two had a restaging laparotomy performed and 21 of these were disease free. If there is complete regression of tumour on CT, MRI is not routinely required. However in the presence of a residual mass MR may be helpful. A rapid decrease in T2 signal intensity that occurs in 80% of cases indicates that the mass is not active. If the mass decreases in size and there is homogeneous low signal intensity on T2 this suggests a good response although

microscopic tumour may be present. If the size decreases but the pattern is homogeneous, hyper-intense or heterogeneous this suggests a partial response. However, inflammation and necrosis will give a similar pattern and a false-positive MR is most likely to happen in the first 4 months post-therapy. Even if the size decreases, but areas of high signal develop this indicates recurrence and these changes may precede symptoms by 8–12 weeks.

Identification of active disease may be helped by the use of functional imaging with ^{67}Ga or PET. When used to look specifically at patients with post-therapy residual masses ^{18}FDG PET has a high predictive value[12]. No patient with a negative scan relapsed within the median follow-up period of 63 weeks. Occasional false-positive results have occurred, some due to coincident inflammatory processes outside the residual mass but some within the residual mass itself. This highlights the need for further study of the timing of PET scans after different types of therapy so false positives can be avoided.

Conclusion

At the present time CT remains the mainstay for imaging the response to treatment although there is debate over whether MRI, CT or the functional imaging studies should be used. Residual masses remain a problem and the use of signal intensity on MR and functional imaging may decrease the requirement for biopsy.

References

[1] Vassallo P, Matei C, Heston WDW *et al*. AMI-227 enhanced MR lymphography: usefulness for differentiating reactive from tumor bearing lymph nodes. Radiology 1994; 501–6.

[2] Surbone A, Lango DL, deVitra VT *et al*. Residual abdominal masses in aggressive Non-Hodgkin's lymphoma after combination chemotherapy: significance and management. J Clin Oncol 1988; 6: 1832–7.

[3] Lewis E, Bernardino ME, Salvador PG, Cabanillas FF, Barnes PA, Thomas JL. Post therapy CT detected mass in lymphoma patients: is it viable tissue? J Comput Assist Tomogr 1982; 6: 792–5.

[4] Boiselle PM, Patz EJ, Vining DJ, Weissler R, Sheard JO, McLoud TC. Imaging of mediastinal lymph nodes. CT, MR and FDG-PET. Radiographics 1998; 18: 1061–9.

[5] Glazer G, Lee JKT, Levitt RG *et al*. Radiation fibrosis: differentiation from recurrent tumor by MR imaging. Radiology 1985; 156: 721.

[6] Hill M, Cunningham D, MacVicar D *et al*. Role of magnetic resonance imaging in predicting relapse in residual masses after treatment of lymphoma. J Clin Oncol 1993; 11: 2773–8.

[7] Israel O, Front D, Lam M *et al*. Gallium-67 imaging in monitoring lymphoma response to treatment. Cancer 1988; 61: 2439–41.

[8] Kaplan WD, Jochelson MS, Herman TS *et al*. Gallium-67 imaging: a predictor of residual tumour viability and clinical outcome in patients with diffuse large-cell lymphoma. J Clin Oncol 1990; 8: 1966–70.

[9] Moog F, Bangerter M, Diedrichs CG *et al*. Lymphoma: role of whole body FDG PET in nodal staging. Radiology 1997; 203: 795–800.

[10] Moog F, Bangerter M, Diedrichs CG *et al*. Extranodal malignant lymphoma: detection with FDG PET versus CT. Radiology 1998; 206: 475–81.

[11] Hoh CK, Glaspy J, Rosen P *et al*. Whole body FDG PET imaging for staging of Hodgkin's disease and lymphoma. J Nucl Med 1997; 38: 343–8.

[12] Cremerius U, Fabry U, Neuerburg J *et al*. Positron emission tomography with 18F-FDG to detect residual disease after therapy for malignant lymphoma. Nucl Med Commun 1998; 19: 1055–63.

[13] Radford JA, Cowan RA, Flanagan M *et al*. The significance of residual mediastinal abnormality on the chest radiograph following treatment for Hodgkin's disease. J Clin Oncol 1988; 6: 940–6.

[14] Rahmouni A, Tempany C, Jones R, Mann R, Yang A, Zerhouni E. Lymphoma. Monitoring tumor size and signal intensity with MR imaging. Radiology 1993; 188: 445–51.

[15] Jochelson M, Mauch P, Balikian J, Rosenthal D, Canellos G. The significance of the residual mediastinal mass in treated Hodgkin disease. J Clin Oncol 1985; 3: 637–40.

[16] Fuks JZ, Aisner J, Wiernik PH. Restaging laparotomy in the management of the non-Hodgkin lymphomas. Med Pediatr Oncol 1982; 10: 429–38.

[17] Stewart FM, Williamson BR, Innes DJ, Hess CE. Residual tumor masses following treatment for advanced histiocytic lymphoma — diagnostic and therapeutic implications. Cancer 1985; 55: 620–3.

[18] North LB, Fuller LM, Sullivan Halley JA *et al*. Regression of mediastinal Hodgkin disease after therapy: evaluation of time interval. Radiology 1987; 164: 599–602.

[19] Nyman RS, Rehn SM, Glimelius BL, Hagberg HE, Hemmingsson AL, Sundstrom CJ. Residual mediastinal masses in Hodgkin disease: prediction of size with MR imaging. Radiology 1989; 170: 435–40.

[20] Lee CKK, Bloomfield CD, Goldman AI, Levitt SH. Prognostic significance of mediastinal involvement in Hodgkin disease treated with curative radiotherapy. Cancer 1980; 46: 2403–9.

[21] Luber GD, Siegel MJ. Mediastinal Hodgkin disease in children: response to therapy. Radiology 1993; 189: 737–40.

[22] Fletcher BD, Xiong X, Kauffman WM, Kaste SC, Hudson MM. Hodgkin disease: use of Tl-201 to monitor mediastinal involvement after treatment. Radiology 1998; 209: 471–5.

[23] Kissin CM, Husband JE, Nicholas D, Eversman W. Benign thymic enlargement in adults after chemotherapy. CT demonstration. Radiology 1987; 163: 67–70.

[24] Heron CW, Husband JE, Williams MP. Hodgkin disease: CT of the thymus. Radiology 1998; 209: 471–5.

[25] Pappa VI, Hussain HK, Reznek RH *et al*. Role of image guided core needle biopsy in the management of patients with lymphoma. J Clin Oncol 1996; 14: 2427–30.